Food protein-induced enterocolitis syndrome

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Purpose of review

To review current knowledge and recent advances in food protein-induced enterocolitis syndrome (FPIES).

Recent findings

Rice is the most common solid food causing FPIES. Rice FPIES is associated with more severe reactions than other foods. Infants presenting acutely may be hypothermic ($<36^{\circ}C$) and have thrombocytosis. Finding of hypoalbuminemia and weight gain less than 10 g/day helps to differentiate chronic infantile cow's milk FPIES from infectious causes. Gastric juice leukocytes more than 10 cells per high-power field are found in infants with positive oral food challenge to cow's milk.

Summary

FPIES is a non-IgE-mediated gastrointestinal food hypersensitivity disorder. Food protein-activated intestinal lymphocytes elaborate inflammatory cytokines that result in increased intestinal permeability, malabsorption, dysmotility, emesis, diarrhea, pain, and failure to thrive. Decreased intestinal transforming growth factor beta and increased TNFα may be important in FPIES. Cow's milk and soy are the most common causes of FPIES, but cereal grains (rice, oat, and barley), fish, poultry, and vegetables may also cause FPIES. The majority of FPIES resolve by age of 3 years.

Keywords

cow's milk allergy, food protein-induced enterocolitis syndrome, milk allergy, rice allergy, soy allergy

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Introduction

Food protein-induced enterocolitis syndrome (FPIES) is non-IgE-mediated gastrointestinal food hypersensitivity. Prevalence of FPIES is not known; in general, gastrointestinal immune reactions to cow's milk (milk) proteins that are mediated by T lymphocytes with or without contribution of specific IgE antibody account for up to 40% of milk protein hypersensitivity in infants and young children [1–3]. FPIES is established as a distinct clinical entity but its features, particularly in the chronic form, overlap with allergic proctocolitis, food protein-induced enteropathy, and allergic eosinophilic gastroenteropathies (Table 1). Allergy tests detecting food-specific IgE antibodies are negative; diagnosis relies on responses to elimination diets with resolution of symptoms, oral food challenges (OFCs) with reappearance of symptoms, as well as exclusion of other causes (Table 2).

Clinical manifestations

FPIES manifests as profuse emesis and diarrhea in young infants and is most commonly caused by milk and soy [2]. Rubin [4] reported intestinal bleeding due to milk allergy in newborns. Gryboski *et al.* [5,6] and Powell [7,8] described infants presenting in the first 6 weeks of life with recurrent vomiting, bloody diarrhea, and abdominal distension while being fed with milk-based formula. Powell [9] characterized major features, established criteria for the diagnosis of milk-induced enterocolitis, and a standard challenge protocol. Reports of a series of infants with FPIES by Sicherer *et al.* [10] (16 patients) and Burks *et al.* [11] (43 patients) further characterized clinical features and refined food challenge protocols. Additional reports [12–16,17•,18] identified solid foods as triggers for FPIES.

Cow's milk and soy food protein-induced enterocolitis syndrome

FPIES is caused by milk or soy in formula-fed infants, with over half reacting to both foods. Symptoms start within first days to 12 months of life; later onset is associated with delayed introduction of milk or soy in breast-fed infants [7,8]. There are no reports of FPIES to milk and soy in infants exclusively breast-fed and no reports of the reactions to the offending foods in the breast milk, suggesting an important protective role of breast feeding in FPIES [12].

In the most severe cases, symptoms start within first days of life with bloody diarrhea, lethargy, abdominal

Table 1 Food protein-induced gastrointestinal syndromes

	FPIES	Proctocolitis	Enteropathy	Eosinophilic gastroenteropathies[a]
Age at onset	1 day–1 year	1 day–6 months	Dependent on age of exposure to antigen, cow's milk and soy up to 2 years	Infant to adolescent
Food proteins implicated				
Most common	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy, egg white, wheat, peanut
Less common	Rice, chicken, turkey, fish, pea	Egg, corn, chocolate	Wheat, egg	Meats, corn, rice, fruits, vegetables, fish
Multiple food hypersensitivities	>50% both cow's milk and soy	40% both cow's milk and soy	Rare	Common
Feeding at the time of onset	Formula	>50% exclusive breast-feeding	Formula	Formula
Atopic background				
Family history of atopy	40–70%	25%	Unknown	~50% (often history of eosinophilic esophagitis)
Personal history of atopy	30%	22%	22%	~50%
Genetics	Unknown	Unknown	Unknown	Unknown
Symptoms				
Emesis	Prominent	No	Intermittent	Intermittent
Diarrhea	Severe	No	Moderate	Moderate
Bloody stools	Severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Laboratory findings				
Anemia	Moderate	Mild	Moderate	Mild–moderate
Hypoalbuminemia	Acute	Rare	Moderate	Mild–severe
Methemoglobinemia	May be present	No	No	No
Acidemia	May be present	No	No	No
Allergy evaluation				
Food prick skin test	Negative[b]	Negative	Negative	Positive in ~50%
Serum food-allergen IgE	Negative[b]	Negative	Negative	Positive in ~50%
Total IgE	Normal	Negative	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Present in <50%
Biopsy findings				
Villous injury	Patchy, variable	No	Variable, ↑ crypt length	Variable
Colitis	Prominent	Focal	No	May be present
Mucosal erosions	Occasional	Occasional, linear	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltrates, papillary elongation and basal zone hyperplasia
Food challenge	Vomiting in 3–4 h; diarrhea in 5–8 h	Rectal bleeding in 6–72 h	Vomiting, diarrhea, or both in 40–72 h	Vomiting and diarrhea in hours to days
Treatment	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3–10 days; rechallenge in 1.5–2 years	Protein elimination, symptoms clear in 3 days with casein hydrolysate, resume/continue breast-feeding on maternal antigen-restricted diet	Protein elimination, symptoms clear in 1–3 weeks, rechallenge and biopsy in 1–2 years	Protein elimination, good response to casein hydrolysate, excellent response to elemental diet, symptoms clear within 2–3 weeks, excellent acute response to steroids; rechallenge and biopsy in 1–2 years
Natural history	Cow's milk: 60% resolved by 2 years Soy: 25% resolved by 2 years	Resolved by 9–12 months	Most cases resolve in 2–3 years	Typically a prolonged, relapsing course
Reintroduction of the food	Inpatient food challenge	At home, gradually advancing from 1 oz to full feedings over 2 weeks	Home, gradually advancing	Home, gradually advancing

FPIES, food protein-induced enterocolitis syndrome.
[a] Eosinophilic gastroenteropathies encompass esophagitis, gastritis, gasteroenterocolitis.
[b] If positive, may be a risk factor for persistent disease.

Table 2 Differential diagnosis of food protein-induced enterocolitis syndrome

Food specific	Food nonspecific
Food protein-induced proctocolitis	Necrotizing enterocolitis
Food protein-induced enteropathy	Sepsis
Eosinophilic gastroenteropathies	Gastrointestinal infection (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia sp*., parasites)
Cow's milk-induced gastroesophageal reflux	Hirschprung's disease
	Intususception
	Volvulus
	Anal fissure

distension, weight loss, dehydration, metabolic acidosis, anemia, elevated white blood cell count with eosinophilia, and hypoalbuminemia [7,19]. Intramural gas may be seen on abdominal radiographs, prompting a diagnosis of necrotizing enterocolitis, sepsis evaluation, and treatment with antibiotics [7,19,20]. Ileus resulting in laparoscopy was reported [21–24]. Overall 75% of infants with FPIES appear acutely ill. About 15% are hypotensive and require hospitalization.

Transient methemoglobinemia was reported in about 35% of young infants with severe reactions and acidemia; some infants required treatment with methylene blue and bicarbonate [10,25,26]. Murray and Christie [25] postulated that methemoglobinemia was caused by an elevation of nitrites resulting from severe intestinal inflammation and reduced catalase activity. Mehr *et al.* [27] reported that 24% of acute FPIES episodes in young infants manifested with hypothermia less than 36°C. Among those with a recorded complete blood count, 65% had thrombocytosis more than 500×10^9/l [27]. Marked thrombocytosis was also noted in additional case reports [24,26].

Symptomatic infants improve promptly when placed on intravenous fluids or with casein hydrolysate-based formula. Food reintroduction induces dramatic symptoms, including shock in 15–20%. In Powell's [8] experience, repetitive emesis started within 1–2 h following ingestion and diarrhea within 2–10 h (mean onset, 5 h) with blood, mucous, leukocytes, eosinophils, and increased carbohydrate content in the stool. Peripheral blood neutrophil counts were elevated in all positive challenges, peaking at 6 h with a mean increase of 9900 cells/μl; range, 5500–16 800 cells/μl. The typical features of cow's milk and soy FPIES are summarized in Table 3.

Solid food protein-induced enterocolitis syndrome

FPIES may be caused by ingestion of solid foods such as rice, oat, barley, chicken, turkey, egg white, green pea, and peanut [12–16,17•,18]. Rice is the single most common solid food inducing FPIES [17•] (Table 4).

Among infants with solid food FPIES, 65% were previously diagnosed with milk, soy, or both FPIES and fed with casein hydrolysate or amino acid-based formula; 35% were breast-fed [12]. Mean age at onset of solid food FPIES tends to be higher than the mean age of onset of milk and soy FPIES [12,17•]. Infants often present

Table 3 Clinical characteristics of cow's milk and soy food protein-induced enterocolitis syndrome

General	Chronic manifestations during continued ingestion of the food	Acute manifestations following ingestion following a period of avoidance
Age at onset: days–12 months	Intermittent emesis	Repetitive emesis, onset 1–3 h following ingestion
Allergy to cow's milk and soy: 65%	Chronic watery diarrhea with blood and mucous	Diarrhea, onset about 5 h following ingestion
FPIES to solid foods: 25%	Carbohydrate malabsorption (stool positive for reducing substances)	Lethargy, dusky appearance
Resolution by age 3 years:	Lethargy	Hypothermia <36°C in 24%
Cow's milk: 65%	Dehydration	Acidemia, methemoglobinemia, and hypotension in 15%
Soy: 25–35%	Hypotensive shock (15%)	Thrombocytosis $>500 \times 10^9$/l
Male:female: 60 : 40	Acidemia	Elevated PMN count
Personal history of atopy	Methemoglobinemia/clinical cyanosis	Frank or occult fecal blood
Atopic dermatitis: 25%	Anemia	Sheets of leukocytes and eosinophils in stool
Asthma/allergic rhinitis: 20%	Elevated white blood cell count with eosinophilia	Abdominal distension, hypoactive bowel sounds, and ileus (extreme cases, typically newborns and young infants <3 months of age)
Family history of atopy: 80%	Hypoalbuminemia	
Family history of food allergy: 20%	Failure to thrive	
Genetics: unknown	Abdominal distension, hypoactive bowel sounds, ileus	
Allergy evaluation		
Prick skin test: negative		
Serum food-IgE: negative		
Tolerated diet: breast milk, extensively hydrolyzed casein formula, amino acid formula		

FPIES, food protein-induced enterocolitis syndrome; PMN, polymorphonuclear.

Table 4 Clinical characteristics of solid food protein-induced enterocolitis syndrome

Feature	Cereal [12,14,17•]	Fish [13]	Poultry [12,16,17•]	Legumes[a] [12,16]
Specific foods (# of patients)	Rice – 30 Oat – 11 Barley – 2	$n=14$; hake, sole, cork float	Chicken – 6 Turkey – 3	Green pea – 3 String bean – 2 Lentil – 1
Age of onset, months; median (range)	6 (3–6)	10.5 (9–12)	6.5 (3–12)	6 (4.5–8)
Sex (% male)	50	42	60	80
# of reactions prior to diagnosis, median (range)	2 (1–5)	3 (2->6)	NS	1 (1–3)
% FPIES to multiple foods	~09	NS	80	80
Other food from the same food group	50	70	33	20
Soy	~06	NS	40	80
Cow's milk	~03	NS	40	60
Both cow's milk and soy	~03	NS	20	40
% Positive prick skin test	0	NS	0	0
% Detectable serum food-IgE	~8 (1/13)	~7 (1/14)	0	0
% Resolved by age 3 years	Rice 50 (6/12) Oat 66 (4/6)	30% resolved in 1–7 years	20	60

FPIES, food protein-induced enterocolitis syndrome; NS, not specified.
[a] Other than soybean.

with multiple reactions and extensive evaluations for alternative causes (infectious, toxic, and metabolic) before the diagnosis of FPIES is established [12,14, 16,17•]. Delayed diagnosis may be explained by common perception that grains, for example, rice, oat, and vegetables, have low allergenic potential and are not considered as a cause of severe food allergic reactions, as well as lack of definitive diagnostic tests and the unusual nature of symptoms. Mehr *et al.* [17•] reported that infants with rice FPIES had severe symptoms and were more likely to receive fluid resuscitation upon presentation than those with milk or soy FPIES (42 versus 15%, $P=0.02$).

In adults, crustacean shellfish (shrimp, crab, and lobster) and fish hypersensitivity may provoke a similar syndrome with severe nausea, abdominal cramps, protracted vomiting, and diarrhea [1].

Diagnosis of food protein-induced enterocolitis syndrome

Diagnosis relies on history, clinical features, exclusion of other causes, and food challenge (Table 5 [3,9–11,28]). Over 90% of patients have negative skin prick tests and undetectable food-specific IgE [10,11]. Hypoalbuminemia and weight gain less than 10 g/day were identified as independent predictors of milk FPIES in young infants with chronic symptoms [29]. Although OFC is the gold standard for diagnosing FPIES, most infants do not need to undergo confirmatory challenges, especially if they have a classic history of severe reactions and become asymptomatic following elimination of the suspected food. However, OFCs are necessary to monitor when a patient 'outgrows' FPIES.

Stool examination in infants with chronic diarrhea may show occult blood, intact polymorphonuclear neutrophils, eosinophils, Charcot–Leyden crystals, and reducing substances; however, these findings are not specific to FPIES.

Recently, atopy patch test (APT) was evaluated in 19 infants (age, 5–30 months), with FPIES confirmed by an OFC [30]. APT predicted the outcome of an OFC in 28 of 33 instances; all positive OFCs had a positive APT, but five patients with positive APT did not react to an OFC. Similar results have not been reported by other investigators, so at this time, the role of APT in the diagnosis of FPIES requires further evaluation.

Endoscopic examination is not performed routinely in FPIES. However, prior to establishment of diagnostic

Table 5 Oral food challenge in food protein-induced enterocolitis syndrome

Challenge protocol
High-risk procedure, requires immediate availability of fluid resuscitation, secure intravenous access
Baseline peripheral neutrophil count
Gradual (over 1 h) administration of food protein 0.06[a]–0.6 g/kg body weight, generally not to exceed total 3 g protein or 10 g of total food for an initial feeding
If no reaction in 2–3 h, administer a regular age appropriate serving of the food followed by several hours of observation
Majority (>50%) of positive challenges require treatment with intravenous fluids and steroids
Criteria for a positive challenge
Symptoms
Emesis (typically in 2–4 h)
Diarrhea (typically in 5–8 h)
Laboratory findings
Fecal leukocytes
Fecal eosinophils
Increase in peripheral neutrophil count >3500 cells/μl peaking at 6 h
Gastric juice leukocytes >10 cells/hpf
Interpretation of the challenge outcome
Positive challenge – three of five criteria positive
Equivocal – two of five criteria positive

[a] Lower dose recommended in children with history of previous severe reaction. Data from [3,9–11,28].

criteria, endoscopy in symptomatic infants with cow's milk, soy, or both FPIES showed rectal ulceration and bleeding with friability of the mucosa. In infants with chronic diarrhea, rectal bleeding, failure to thrive radiographs, or both showed air fluid levels, nonspecific narrowing and thumb printing of the rectum and sigmoid, and thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid [21,31]. In the cases of ileus, in which laparotomy was performed, distention of small bowel loops and thickening of the wall of jejunum distal to Treitz's ligament with diffuse subserosal bleeding was observed [21,22]. Follow-up studies performed in asymptomatic patients on a restricted diet documented resolution of radiological abnormalities.

Oral food challenge in food protein-induced enterocolitis syndrome

OFCs can be used to establish the diagnosis of FPIES or to evaluate the possibility that FPIES has been 'outgrown'. Follow-up challenges are usually recommended every 18–24 months in patients without recent reactions [3]. Korean investigators [32] reported that among 27 infants with milk FPIES, 64% tolerated milk at 10 months and 92% tolerated soy at 10 months. They suggested that in milk FPIES, the first milk challenge should be done at an age of more than 12 months, whereas the first soy challenge could be done between 6 and 8 months.

Guidelines for preparation and interpretation of the OFC for FPIES are summarized in Table 5. Oral challenge involves the administration of food protein, 0.06–0.6 g/kg body weight, with lower doses (0.06 g/kg) used in children with prior severe reactions [9,10]. Generally, the amount served initially during an OFC does not exceed 3–6 g of food protein or 10–20 g of total food weight (usually less than 100 ml of liquid food such as cow's milk or infant formula). Food is divided into three equal portions and served over 45 min [33]. Patient is observed for approximately 2–3 h and if asymptomatic, a second feeding, typically an age-appropriate regular serving amount is given followed by observation for several hours [3]. Food challenge in FPIES should be performed under physician supervision with secure intravenous access for fluid resuscitation [10]. Rapid intravenous hydration (20 ml/kg boluses) is the first-line therapy; however, corticosteroids are often used for severe reactions based on presumed pathophysiology that involves T cell-mediated intestinal inflammation. Epinephrine should be available for severe cardiovascular reactions with hypotension/shock. Our unpublished experience is that prompt administration of epinephrine does not improve the symptoms of emesis and lethargy, which however resolve promptly with vigorous intravenous fluid administration.

Recently, Hwang *et al.* [28] proposed gastric juice analysis as an additional confirmatory test in the equivocal oral challenges. Gastric juice leukocytes higher than 10 cells/hpf were observed in 15 of 16 positive milk challenges after 3 h, including two infants without emesis or lethargy, whereas none of the eighth age-matched control infants had gastric juice leukocytes over 10 cells/hpf. This observation needs to be validated in larger groups of patients.

Dietary management of food protein-induced enterocolitis syndrome

Avoidance of the offending food is recommended. Considering that concomitant milk and soy FPIES occur in over 60% of cases, extensively hydrolyzed casein formulas are recommended for infants that cannot be breast-fed [3,8,10]. Eighty percent of patients with milk, soy, or both FPIES respond to extensively hydrolyzed casein formula with resolution of symptoms within 3–10 days. About 20% of patients require amino acid-based formula or temporary intravenous therapy [34,35].

Proposed guidelines for solid foods introduction to infants with cow's milk or soy FPIES consider that up to one-third of these children appear to develop a reaction to solid food and recommend introduction of yellow fruits and vegetables instead of cereal grains as first foods at 6 months [3,12]. Infants with solid food FPIES are likely to react to other foods, 80% are reactive to more than one food protein, 65% react to milk, soy, or both, and those with a history of reactions to one grain have at least a 50% chance of reacting to other grains. Empirically, infants with solid food FPIES may benefit from avoidance of grains, legumes, and poultry in the first year of life [3]. Introduction of milk and soy in infants without prior history of reactivity to these foods may be attempted at the age of more than 1 year, preferably under physician supervision. Tolerance to one food from each 'high-risk category' such as soy for legumes, chicken for poultry, or oat for grains might be considered as an indication of increased likelihood of tolerance to the remaining foods from the same category [3].

Natural history of food protein-induced enterocolitis syndrome

Sensitivity to milk and soy was lost in 60 and 25% of patients, respectively, by the age of 3 years [10,12]. Rates of resolution of solid food FPIES by the age of 3 years were 40% for rice, 66% for oat, and 67% for other foods (vegetables). Current US experience suggests that soy, cow's milk, and poultry FPIES may have the longest duration [12]. FPIES rarely develops to foods upon first exposure beyond 1 year of age. For example, wheat allergy has not been reported in infants with oat or

rice-induced FPIES, but introduction of wheat was significantly delayed, presumably avoiding the 'window of physiologic susceptibility' for FPIES development [3,12]. Patients presenting initially or developing food-specific IgE antibodies after the diagnosis of FPIES have a more protracted course [10,12]. It may be prudent to include prick skin testing, measurement of serum food-specific IgE level, or both in the initial as well as follow-up evaluations to identify patients at risk for persistent FPIES.

Pathology

Currently, diagnosis of FPIES is based on clinical criteria; endoscopy and biopsy are not performed routinely. Previous endoscopic evaluations and biopsies in infants with FPIES highlight inflammatory responses in the colon, with diffuse colitis and variable ileal involvement. Colon mucosa can be mildly friable or show severe spontaneous hemorrhage, and minute ulcers can be found [3,11,36]. Crypt abscesses are identified in some patients [37]. Jejunal biopsies reveal varying villous atrophy, edema, and increased numbers of lymphocytes, IgM and IgA-containing plasma cells, eosinophils, and mast cells [37,38].

Pathophysiology

It is hypothesized that in FPIES, local inflammation induced upon food allergen ingestion leads to increased intestinal permeability and fluid shift. However, baseline antigen absorption is normal and does not predispose to FPIES [36].

Following in-vitro stimulation with milk or soy proteins, peripheral blood mononuclear cells (PBMCs) from children with FPIES have significantly ($P < 0.01$) higher geometric mean proliferation indices than children with negative oral challenges to cow's milk and soy [39]. Children with milk allergy have higher lymphoproliferative responses than control patients; the response is similar in IgE-mediated milk allergy and milk FPIES [40].

Because TNFα induces neutrophil activation and increases intestinal permeability *in vitro* by altering the tight junctions between epithelial cells; TNFα has been investigated in a number of studies [41]. Heyman *et al.* [42] suggested that TNFα secreted by circulating milk-specific T lymphocytes increased intestinal permeability, thus contributing to the influx of antigen into the submucosa with further activation of antigen-specific lymphocytes. Lower quantities of milk protein required to stimulate TNFα secretion and prolonged secretion of TNFα by PBMCs were reported in patients with active intestinal milk allergy compared with those with cutaneous symptoms and those who outgrew milk allergy [43]. Children with milk allergy had increased stool TNFα concentrations following positive milk challenge.

Chung *et al.* [44•] found depressed transforming growth factor beta (TGF-β) expression in duodenal biopsies from 28 infants with challenge-proven milk FPIES. Expression of type 1 TGF-β receptors was lower in the patients with villous atrophy compared with patients without villous atrophy ($P < 0.001$) and negatively correlated with the severity of villous atrophy ($r = -0.59$, $P < 0.001$). In contrast, TNFα expression on epithelial and lamina propria cells was greater in the patients with villous atrophy ($P < 0.01$), suggesting that imbalance in TGF-β/TNFα may be important in the pathophysiology of FPIES.

Systemic IgE antibody responses are generally not detected in FPIES, although an increase in serum food-specific IgA and IgG antibody levels was noted [45]. Lower levels of serum milk-specific IgG_4 antibody levels ($P < 0.05$) and a trend for higher IgA antibody levels were found in children with milk FPIES when compared with the control group [40]. IgG and IgA antibodies in the pathogenesis of FPIES should be further explored. It is tempting to speculate that specific IgE antibody produced in the intestinal mucosa may play a role in the antigen uptake and local inflammation.

Conclusion

FPIES responds well to dietary elimination of the offending food. Tolerance usually develops within 3 years of life, but occasionally FPIES may persist into the teenage years. Rice is the most common food in solid food FPIES; children may react to many unrelated foods. Diagnosis of FPIES is frequently delayed due to low index of suspicion and lack of confirmatory tests. Heightened awareness and increased attention should lead to early diagnosis and treatment.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 392).

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